NWX-HHS-FDA

Moderator: Irene Aihie
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1:30 pm CT

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session of the call. To ask a question during that time, please press Star then 1 and record your name and company.

Today's conference is being recorded. If you have any objections, you may disconnect at this time.

I'd now like to turn the meeting over to Irene Aihie. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I am Irene Aihie from CDRH's Office of Communication and Education. On May 6, 2015 the draft guidance titled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" published in the Federal Register.

The focus of today's webinar is to help stakeholders understand the framework described in this draft guidance document and provide further clarification where necessary. Your presenters are Kathryn O'Callaghan, the acting Associate Center Director for Science and Strategic Partnership in the

Office of the Center Director; and Jacqueline Francis, a medical officer from the Office of Device Evaluation.

Following the presentation, we will open the lines for your questions related to topics in the draft guidance only. Please note that questions about specific products should be directed to the appropriate review office. Other CDRH subject matter experts are also available today to assist with the question and answer portion of our webinar.

Now, I give you Katie.

Kathryn O'Callaghan: Thank you Irene and thank you to all of the participants who are joining us today by phone. As Irene mentioned, I'm Acting Associate Center Director for Science and Strategic Partnership, and in that role -- among other things -- I oversee a variety of pediatric activities here at CDRH. And it's my pleasure today to share with you our latest effort in our ongoing commitment to stimulate the innovation and growth in a number of devices that are indicated and labeled for safe and effective pediatric use.

Next slide, please. Thank you.

So our objectives today for the webinar are to provide you with an overview and some context of the proposed framework that's outlined in this draft guidance and to answer any questions you may have about the specific concepts. And the goal for this meeting overall is to enable the provision of more specific and better feedback to the docket on our draft guidance.

The key points I'd like to highlight for you before we delve into the specifics is that as many of you know, particularly if you're involved in this space, there's a recognized need - many unmet needs in the pediatric diagnosis and

treatment of conditions. And medical devices play an important role in the care of these patients; yet there are relatively few devices that are indicated and labeled for such use.

And so this draft guidance proposes the framework for how sponsors can consider leveraging data from adult populations or other pediatric populations to augment what is known about a device's performance in a pediatric patient population. So the approach that we describe in this guidance we believe could stimulate growth in the number of devices that are specifically indicated and labeled for pediatric patients.

The guiding principles that are embodied in our policy and that we will use to guide our implementation are that the draft guidance does not change the threshold for approval or valid scientific evidence. So applications will still need to demonstrate a reasonable assurance of safety and effectiveness or PMA's or safety and probable benefits for HTE's.

But existing clinical data, whether in the adult population or other pediatric populations, may be relevant and may be appropriate for leveraging; and in these cases, use of this data can reduce the amount of prospective data that may be needed in a given pediatric population to arrive at those thresholds for approval. And if not appropriate, no data would be leveraged.

And in our consideration of whether or not a particular data set is appropriate for extrapolation, we would consider these on a case-by-case basis following the decision tree, which is outlined in the draft guidance. And this consideration will be, then, separately for effectiveness endpoints and for safety endpoints.

So with that, I'd like to introduce Dr. (Francis) who was one of the lead authors of this guidance to walk through more of the content.

Dr. Jacqueline Francis: Thank you Katie. Before I begin, I'd like to apologize if there are any errant or escaping sneezes or coughs coming from me. I'm recovering from something (a cold). So please bear with me. I appreciate your patience.

So I'd like to begin to talk today about our outline for the presentation today. I'll be discussing pediatric device challenges, CDRH definition of pediatrics, what is extrapolation and why consider it, the purpose of our guidance and specific objectives, the policy history and stakeholder input, an overview of the key guidance elements, why extrapolate device safety data, the suggested decision process, possible extrapolation decisions, and discuss conclusions and next steps.

There are many challenges in the development of medical devices labeled for pediatric use. We find that typically they are small and diffusely scattered populations of patients and they tend to lead to smaller sample sizes. There are as many challenges in enrolling and considering pediatric patients and that can increase the length of time needed to determine safety and effectiveness.

There are more barriers with pathophysiology, physiology, anatomy, and human factors in children as well within pediatric subpopulations when compared to adults. Reference samples may require small amount - an amount of blood that's too voluminous to obtain safely from a neonate or from a small child.

It's well known that there's extensive off-label use of adult devices without labeling information to promote safe and effective use in pediatric patients. This is another regulatory challenge.

So the CDRH definition of pediatric patients is in line with that of the American Academy of Pediatrics, and that is described as follows. For neonates, those patients are from birth - date of birth twenty-eight days of life; infants -- twenty-nine days to less than two years of age. Children are two years to less than twelve years. Adolescents are age twelve through 21, up through but not including the 22nd birthday. And transitional pediatric patients are age eighteen to 21. Transitional patients can be helpful for groups to extrapolate within pediatric subpopulations.

Please be reminded also that CDRH, CBER and CDER have different definitions of pediatrics. And this is particularly important for any company considering combination devices.

So what is extrapolation? For the purpose of this document, extrapolation refers to the leveraging process whereby the indication for use of a device in a new pediatric population can be supporting by existing clinical data from a studied patient population.

Why consider extrapolation? We hope to stimulate development of and labeling for devices available for United States pediatric patients while ensuring that the approval of these devices is based on valid scientific evidence. We also hope to promote proper labeling and indications for safer and more effective use in pediatric patients; and where possible, we'd like to leverage any available clinical evidence to streamline requirements for establishing a pediatric intended use claim.

To the extent that existing data are relevant and similar to how the devices are expected to perform clinically in the intended pediatric populations, we believe that those data may be leveraged to bolster other valid scientific

evidence including newly collected pediatric data when available. And that is the purpose of the guidance.

The objectives of the guidance are as follows: to increase the availability of safe and effective pediatric devices by leveraging existing relevant clinical data for use in premarket approval applications -- or PMAs -- and humanitarian device exceptions -- or HDEs; to explain the circumstances in which FDA believes it may be appropriate to leverage existing clinical data to support pediatric device implications and labeling; to outline the approach FDA uses to determine whether extrapolation is appropriate and, if so, to what extent the data can be leveraged; and finally to describe the statistical methodology that will be used or can be used to leverage the data in a way that increases the precision for pediatric inferences.

With regard to the policy history, CDRH published a final guidance document in 2004 entitled "Premarket Assessment of Pediatric Medical Devices." This document indicated that data can be extrapolated to support effectiveness and safety for premarket approval applications when consistent with scientific principles.

In 2007, Congress passed the Pediatric Medical Device Safety and Improvement Act which permits the extrapolation of adult effectiveness data to support a pediatric indication in the disease course if the disease course or the effect of the devices in the adults is likely to be the same in children.

In 2011, a workshop was held at FDA to discuss an approach to extrapolation of adult data for pediatric populations, and those participants included stakeholders and FDA staff. Subsequent to that, a CDRH medical officer group was convened to plan the approach for the extrapolation process.

In order to make decisions about the effectiveness and safety of the medical device in pediatric patients, the Food and Drug Administration considers the totality of the evidence available. The scope of the guidance includes medical devices subject to PMA and HDE premarket requirements. This guidance facilitates the efforts to address an unmet medical device need for pediatric patients.

The key elements of the guidance are as follows. This guidance permits the extrapolation of effectiveness and safety data where appropriate. Safety and effectiveness are treated independently for extrapolation purposes. A decision tree outlines how to decide whether or not extrapolation is appropriate and the appendix includes a statistical guidance on potential methods for extrapolation and examples of extrapolation that include six hypothetical examples and one actual example.

So why extrapolate device safety data? Existing clinical data may provide valid scientific evidence about device safety which is relevant to medical device performance in children. The mechanism of action in devices is often expected to be similar in adults and pediatric patients while dosing and PK tend to vary in drugs.

Other forms of scientific evidence may be used to affect many device performance characteristics related to safe device functioning such as preclinical testing, engineering, computer modeling, or other nonclinical data.

And as with any PMA or HDE, FDA will consider clinical data whether extrapolated or not alongside other forms of valid scientific evidence to assess the device performance such as preclinical testing, engineering models, compatibility, virtual patient simulation, literature studies, or case reports in

order to determine whether responses demonstrated have reasonable assurance of safety and effectiveness in the intended pediatric population.

This slide summarizes our decision tree. In our decision tree, we assess the relevancy of adult or pediatric subpopulation data and expected similarity of responses to an intervention related to device characteristics, disease characteristics, and population characteristics. And we also assess data quality. Please refer to Figure One of the draft guidance for the complete decision tree.

This guidance is not designed to outline criteria for approval and this guidance does not change the threshold for regulatory approval or valid scientific evidence.

So with regard to the possible extrapolation decisions, after answering two critical questions of how the disease and the expected response are similar or different between pediatric and adult patients, extrapolation of adult data may be done fully or partially through statistical modeling. In full extrapolation, existing clinical data are used directly as a complete substitute or prospective clinical studies. And in partial extrapolation, existing data are combined via statistical model with pediatric data sources or prospectively collected pediatric data from clinical trials.

The partial extrapolation permits utilization of existing clinical data to support demonstration of device safety or effectiveness for use in pediatric patients with the expectation that some pediatric data are necessary. The existing clinical data bolster any new clinically collected pediatric data. If it's not appropriate or it's insufficient to meet the threshold of valid scientific evidence, data will not be extrapolated.

So in conclusion, despite a recognized need for relatively few medical devices to have pediatric-specific indications and labeling. This draft guidance proposes a framework to consider leveraging adult data to augment what is known about the devices' performance in pediatric patients. The approach described in this draft guidance we hope can stimulate the growth in the number of devices specifically indicated and labeled for pediatric patients.

With regards to next steps, we hope that you will consider public comments to this docket. The docket number is listed on the slide. And with regard to implementation of this process, CDRH will use a pediatric group of experts within the Center to evaluate any applications that suggest the use of extrapolation.

And yes, now the lines are open. We'll take any questions that you might have. Thank you.

Coordinator: Thank you. We will now begin the question and answer session. If you'd like to ask a question, please record your - please press Star 1 and record your name and company name. Once again, to ask a question, please press star, then 1.

One moment, please, while we wait for the first question.

Our first question comes from Laura Henze Russell with Precision Health.

Laura Henze Russell: Yes. Can you hear me?

Dr. Jacqueline Francis: Yes, we can hear you.

Laura Henze Russell: Okay, great. I have a bit of that horrible cold too, so forgive my voice. I have another consideration that I wonder if you're looking at, which is that the ability of different children and adults to tolerate medical devices of various materials varies by their genetic status. And I know for other products it can vary a lot based on how well an individual metalates which is related, again, to their genetic and epigenetic changes.

So I know I've been working to advocate for more attention to basket studies, both premarket and post-approval, to understand why devices might be good for, say, sixty or even eighty percent of the population but not good for twenty percent; and I believe that, actually, the ability to tolerate some of the devices declines with age.

And there are studies that show immediate harm to boys with certain gene types from certain devices that already have FDA clearance. And so I'm concerned if you're not using a precision medicine framework and basket studies to look at how device tolerance varies by metalation status; and in children, the consequences could be concerning.

Was that clear?

Dr. Jacqueline Francis: Yes, you were clear. Excuse me, I was blowing my nose.

So with regard to your question, the understanding, of course, between the genetics between adults and pediatrics would be - that's something that we would consider, again, with our decision tree. Maybe I should back up.

Have you had a chance to review the guidance?

Laura Henze Russell: No. I've been sick and I have a ninety-five year old aunt in and out of the hospital, so I'm a bit behind. I will look at that. I just - maybe it's a broader question. I'm glad to be seeing it done now, but how do we get this done for some currently approved devices that are not safe for pediatrics as well as adult patients because of their genetic status? And so - and it's - that is in these guidelines going forward now.

Katie: Thank you for your comment and I think if there are particular products that you have in mind we'd be happy to follow up with you. I'd request that you direct an inquiry to the email address that's shown on the screen there. The Division of Industry and Consumer Education will be able to follow up with you after the call. Thank you.

Laura Henze Russell: Is that the CDRH Learn one? Yes, okay. Great, thank you.

Coordinator: The next question comes from (Donald Craft) with (Stadro).

(Donald Craft): Yes, hello. We are curious as to whether this guidance could be considered applicable for 510K applications that require clinical data; specifically in the area of in vitro diagnostics.

Dr. Jacqueline Francis: Thank you for your question. The purpose of this guidance is pretty much limited to PMAs and HDEs only.

(Donald Craft): So why were 510Ks excluded?

Dr. Jacqueline Francis: The - as far as the pediatric - well, with regard to Congress and the law itself, it only included PMAs and HDEs. So 510Ks were not within scope of the reg itself.

Katie: That being said, if there's a specific product that you have in mind for which you think scientific rationale can be provided following some of the concepts that are outlined in this guidance, I would encourage you to contact your review division and open that dialogue with them directly.

(Donald Craft): So it wouldn't be appropriate to, during the pre-sub process, broach this subject?

Katie: Yes it would, and also I would encourage you to make your comment regarding the scope of the guidance to the docket. That will allow us to include that in our formal consideration of public comments, and that will be helpful to hear.

(Donald Craft): Okay. Thank you.

Dr. Jacqueline Francis: Thank you.

Coordinator: And as a reminder, to ask a question please press Star 1, and please make sure you record your first and last name and your company.

The next question comes from Isabelle Banville with Physio-Control.

Isabelle Banville: Hi. I was wondering if it would be within the scope of this webinar to have someone walk us through Figure 1 -- the extrapolation decision tree -- maybe with a hypothetical or even just walking us through what's intended with each of the statements for clarification.

Dr. Jacqueline Francis: Thank you for your question. I think rather than devoting a large chunk of time to that, I'll point you to the text in the section immediately following the figure. What we've done there is actually walk through each of

the decision points in question using some hypotheticals. So that will hopefully help to illustrate how we mean to implement this.

And again, in the appendix section you can actually see some hypothetical examples as well as an actual example. There's also some statistical guidance as well in case that's your background.

Are you still there?

Isabelle Banville: Yes. I got the comments. Thank you.

Dr. Jacqueline Francis: Okay, thank you.

Coordinator: Next question comes from (Barbara Knuckle) with Abbott Laboratory.

(Barbara Knuckle): Yes, I'm just curious. You mentioned that CBER and CDRH has different definitions of pediatrics. And since sometimes PMAs are - go to both branches, I'm just wondering why you have different definitions.

Dr. Jacqueline Francis: Well, I think those are essentially - they're different centers and so it's within the rights of each center to determine their own definitions based on their product lines. So CBER and CDRH all have different definitions for pediatrics, unfortunately, and I recognize that could be a challenge with regard to regulating combination products, as I mentioned earlier. But unfortunately, that's just the way at this land and FDA.

And if you'd like, please submit a comment to the docket with regard to your comments.

(Barbara Knuckle): Sure. Thank you.

Dr. Jacqueline Francis: You're welcome.

Coordinator: Next question comes from Deborah Ladenheim with Catalyst.

Deborah Ladenheim: Yes, hello. This is a very similar question to the one that was just asked. I was just wondering whether this draft guidance also refers to those devices that are regulated under CBER as well as those with CDRH.

Dr. Jacqueline Francis: Thank you for your question. Yes, it does. [ADDITIONAL CLARIFICATION TO RESPONSE: The draft guidance applies to combination devices with CDRH and CBER but does not apply to CBER products across the board]

Deborah Ladenheim: Thanks.

Coordinator: As a reminder, to ask a question, please press Star and then 1.

Next question comes from (Scott Mendretta) with (Cyberonics).

(Scott Mendretta): Hi, yes. My question was that it looks like the device should already be FDA approved or cleared for adults. And I was wondering why we wouldn't be able to put in the application for both indications with the adult data if we were going to be able to use the adult data anyway for the pediatric indication.

Katie: Thank you for your question. I'm glad that you asked it. We certainly did not intend to limit the application of this guidance to only products that already have an approval for adult indications. In fact, we would recommend that if you think that you would be able to leverage adult data or data from another pediatric population that you come and speak with us early about the plans for

doing that and the rationale for why leveraging the data is appropriate. That can absolutely be planned before submitting a marketing application at all.

Does that answer your question?

(Scott Mendretta): Yes, thank you.

Dr. Jacqueline Francis: Thank you.

Coordinator: Currently there are no further questions.

Irene Aihie: Thank you. This is Irene Aihie and we appreciate your thoughtful questions and participation today. if you have any additional questions, please direct all questions to (Dice)@fda.hhs.gov.

Today's presentation and transcript will be made available by Wednesday, May 27 on the CDRH Learn Web page at www.fda.gov.

It seems that we have an additional question.

Coordinator: Next question comes from Laura Henze Russell with Precision Health.

Laura Henze Russell: Yes, I was - I did miss the session a few months ago on UDIs, which I think is a great move, and I just had one question if you could direct me to the best person at the agency to ask this. Will UDIs be required on all installed devices, even ones that have prior been approved?

Katie: Thank you so much for that question. If you could please refer that question to the email address on the slide, that's (dice)@fda.hhs.gov. And someone will definitely get back to you.

Laura Henze Russell: Okay, thank you so much.

Woman: You're very welcome.

Irene Aihie: Okay. Seeing that there are no other questions, thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on Wednesday, May27 on the CDRH Learn Web page at www.fda.gov/training/cdrhlearn. If you have any additional questions about the draft guidance document, please use the contact information provided at the end of the slide presentation.

As mentioned earlier, FDA welcomes your comments and suggestions on this draft guidance. You may provide comments to the docket. Docket number FDA-2015-D-1376. The comment period will close on August 6, 2015. As always, we appreciate your feedback.

Again, thank you for your participation and this concludes today's webinar.

Coordinator: Thank you for your participation in today's conference. Please disconnect at this time.

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